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Topical Zhiyang Pingfu Liquid for Moderate to Severe Skin Rash Associated With EGFRIs: A double-blinded randomized controlled trial

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Abstract

Background: Skin rash is the most common adverse effect associated with epidermal growth factor receptor inhibitors (EGFRIs). The study has observed the efficacy and safety of Zhiyang Pingfu Liquid in the treatment of EGFRIs-related moderate and severe rash. **Methods:** Patients suffering from EGFRIs-related moderate to severe rash were enrolled and then randomly divided into the treatment group and the control group, receiving Zhiyang Pingfu Liquid and placebo liquid respectively combined with minocycline and methylprednisolone recommended by guideline for 14 days. Changes in rash grades were observed, as well as the dosage of minocycline. Blood routine examination and liver and kidney function were evaluated to observe the safety of Zhiyang Pingfu Liquid. The total response of rash included complete response (CR) and partial response (PR). And the effective rate of rash was the percentage of CR and PR in the total cases. **Results:** A total of 54 out of 58 patients finished the study with 27 patients in each group. The effective rates of rash among the treatment group and the control group were 81.48% and 55.56% after 14 days treatment ($P = .040$). The treatment group had a lower dosage of minocycline compared with the control group. The median total dose of oral minocycline administration was 1000 mg in the treatment group and 1400 mg in the control group. **Conclusion:** Zhiyang Pingfu Liquid can effectively improve the moderate and severe EGFRIs-induced rash, and reduce the use of minocycline, as well as the side reactions brought by minocycline. However, larger randomized controlled trials are needed to verify these findings. **Clinical Trial Registration:** The trial was registered on the Chinese Clinical Trial Registry, the registration number is ChiCTR1800017053.

Keywords

epidermal growth factor receptor inhibitors, adverse events, rash, Zhiyang Pingfu Liquid, randomized controlled trial

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Introduction

Rash is one of the most common adverse effects of epidermal growth factor receptor inhibitors (EGFRIs) with an incidence of 67.2% to 76.3%.[1] In phase III studies[2] with cetuximab, the reported incidence of rash ranged from 88% to 90%. EGFRIs-related rash usually occurs in densely distributed areas of the human sebaceous glands such as the head, face, and chest, accompanying symptoms such as pruritus or pain.[3] It is more probable that erythema or pigmentation remains after rash.[4] Antibiotics and corticosteroids are recommended by guidelines[5] to treat moderate to severe rash, but the dissatisfaction with efficacy remains, and side effects limit the clinical use. Traditional Chinese medicine (TCM) is another choice to treat EGFRIs-related

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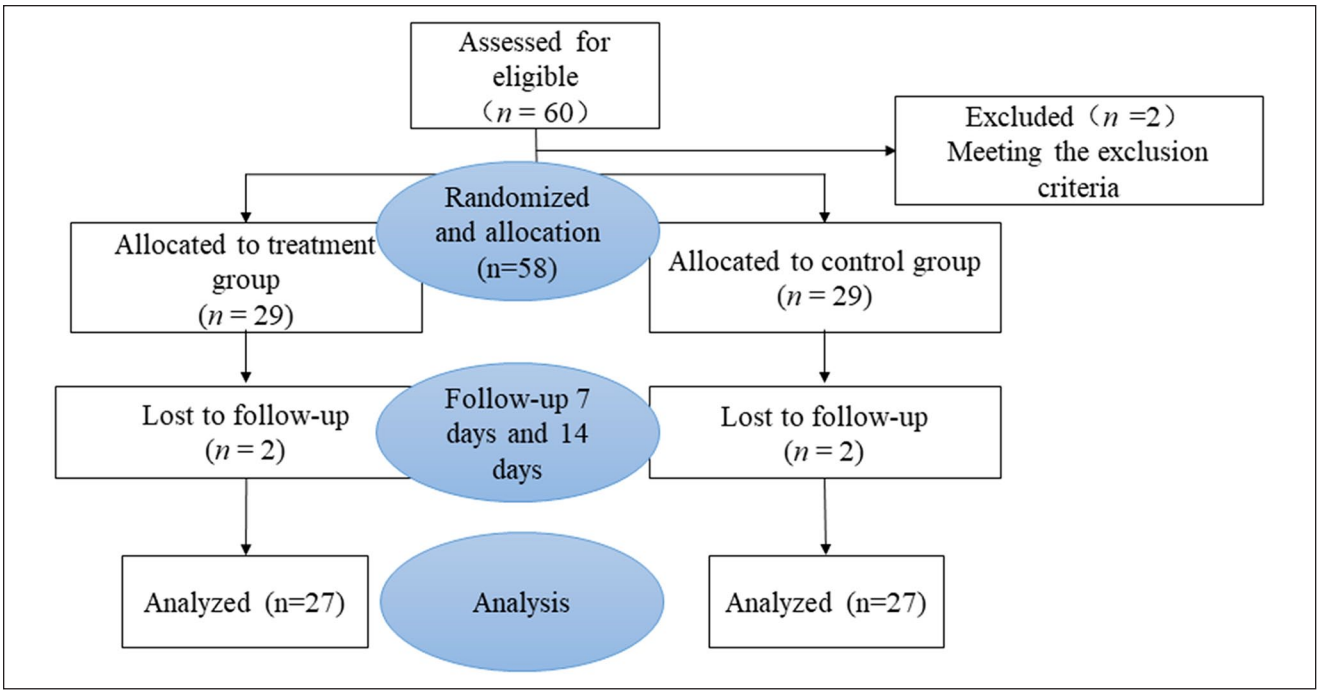

Figure 1. Flowchart of clinical case inclusion.

rash. Zhiyang Pingfu Liquid has been used in clinical practice to treat EGFRIs-related rash for more than 8 years as an empirical formula, and its efficacy and safety have been clinically verified. The drugs used in this study were provided and controlled by the Pharmacy Department of China-Japan Friendship Hospital, and their main components were identified by ultra-high liquid chromatography. In this study, a double-blind randomized controlled trial was designed to investigate the efficacy and safety of Zhiyang Pingfu Liquid in patients with moderate to severe rash induced by EGFRIs.

Methods

Design

This study was a double-blind, randomized, placebo-controlled clinical study. The patients were enrolled from China-Japan Friendship Hospital. The trial was registered in Chinese Clinical Trial Registry. The registration number is ChiCTR1800017053.

Ethical Approval

The trial was performed with the approval of the Ethics Committee of China-Japan Friendship Hospital for Drug/Instrument Clinical Researches (2018-83-K58). All patients signed an informed consent form before randomization and treatment.

Participants

A total of 58 patients were enrolled (Figure 1), who were randomized to receive Zhiyang Pingfu Liquid or placebo in an allocation ratio of 1:1.

Eligible patients had to meet the following inclusion criteria: (a) patients with malignant tumor confirmed by pathology or cytology; (b) patients with application of EGFRIs who developed EGFRIs-related rash; (c) age above 18 years, Karnofsky score (KPS) above 60 points, expected survival duration more than 3 months[6]; (d) patients with rash grade 2 (moderate) or above according to Multinational Association of Supportive Care in Cancer (MASCC); symptoms lasted for more than 1 day; (e) no intellectual and psychiatric disorders, normal language ability and able to cooperate for symptom assessment and quality of life scoring; and (f) patients understand and agree to receive the treatment, and sign informed consent form.

Exclusion criteria were the following: (a) patients with EGFRIs discontinuation; (b) patients with no rash or grade 1 (mild) rash according to MASCC; (c) patients with other skin diseases; (d) patients with other serious complications, such as severe heart, liver or kidney failure; (e) patients with allergic constitution; and (f) patients with poor compliance.

Outcomes and Endpoints

The primary endpoint was the effective rate in each group. The rash was evaluated by MASCC[7] grading systems. The

efficacy evaluation was in accordance with the consensus of the EGFRI Dermatologic Toxicity Forum.[8] Complete response (CR) was defined as dermatologic toxicities disappearing without subjective symptoms, sign of superinfection, and impact on activities of daily life; partial response (PR) was defined as the grade of dermatologic toxicities was lowered 1 grade or more; no response (NR) was defined as the grade of dermatologic toxicities had no changes or proceeded to higher grades. The effective rate of rash was the percentage of CR and PR in the total cases.

The rash of the patients was graded and pictures were taken when they enrolled, with follow-ups at the 7th and 14th treatments.

The secondary endpoints were the dosage of minocycline and methylprednisolone, the score change of pruritus symptoms accompanying rash and the grades changes of other EGFRIs related cutaneous adverse effects such as skin xerosis and paronychia. After the patients were enrolled in the study, we distributed a questionnaire to the patients, and trained them to record their daily medication and adverse events, such as the name of the drug, dosage, and frequency. We connected with patients by WeChat (an instant messaging application) to assess the severity level of the rash and adjust the dosage of antibiotics promptly. Patients came to the hospital on the 7th day and 14th day to undergo follow-up. The questionnaire was reviewed at each follow-up visit by the study group. The routine blood values, liver, and kidney function were observed as safety indicators.

Intervention

Patients in the treatment group received external Zhiyang Pingfu Liquid and the control group received placebo liquid. Both groups were treated with external hydrocortisone cream, combined with oral minocycline. If necessary, methylprednisolone was added to the 2 groups of patients with severe rash.

The Zhiyang Pingfu Liquid consisted of 5 TCM herbals, Radix Scutellariae (黄芩), Radix Sophorae Flavescentis (苦参), Herba Portulalacae(马齿苋), Cortex Dictamni (白鲜皮), and Herba Taraxaci(蒲公英), whose proportion was 3:3:3:2:2. The raw materials of the prescription in proportion are added to water and refluxed to extract twice, each time for 1.5 hours. The decoctions are combined, then filtered, and concentrated. The placebo was made of dextrin, starch syrup as adhesive, caramel pigment as colorant, and bitterant and aspartame as corrigent. They were packed with standardized packaging the same as Zhiyang Pingfu Liquid; the smell and appearance of this drugs were consistent. Zhiyang Pingfu Liquid and placebo were unified preparations by the Pharmacy Department of the China-Japan Friendship Hospital with strict production and quality standards.

The Zhiyang Pingfu Liquid or placebo were applied externally 30 minutes at a time by mask, twice a day for participants, and 0.1% hydrocortisone butyrate cream was externally with half hour interval. The minocycline hydrochloride capsule was taken orally 100 mg twice a day for 14 days, unless the patient had serious adverse events or with a degraded rash, in which case the patient can reduce minocycline dosage as assessed by the researchers. The methylprednisolone tablet was taken orally 20 mg once a day, for 14 days or until the patients had serious adverse events. If the rash had been reduced to mild severity, these 2 kinds of oral medicines could be stopped upon confirmation of the researchers after 14 days.

Randomization and Blinding

A randomization table was generated by a professional statistician unrelated to this trial to randomize enrolled patients into a treatment group or a control group. Neither the researcher nor the patient himself/herself knew the group in which they were included; a third party was asked to code the drugs uniformly according to the randomization table and to sequester the blind base, and the researchers dispensed the drugs according to the coding. Researchers who evaluated the rash were blinded to the group assignment. The placebo could not be identified from the experimental drug. Unblinding was uniform after the end of the trial. If serious adverse events occurred, the emergency of breaking the blind was conducted; the responsible researchers decided whether to open the emergency letter. Once the emergency letter was opened, the case was considered as a case of shedding, not included in the efficacy analysis, but included in adverse reactions analysis.

Sample Size Calculations

According to the test design, this study should be a superiority trial. With the effective rate as the main evaluation index, the sample size calculation referred to the superiority test formula of the independent sample rate of the 2 groups. It was known that the effective rate of placebo was 50.00% from literature review,[9] it was predicted that effective rate of experimental group was 91.00% according to a previous study.[10] For 90% power with α set at 0.05, we calculated 50 participants would be needed by 2-tailed test. Considering 20% as the noncompletion rate, the trial needed 60 participants at all.

Statistical Analysis

Statistical analyses were done using SPSS software version 20.0. The statistical analysis of the differences for each treatment and control group was carried out using the Student's *t*-tests for continuous variables with χ^2 for the

Table 1. Patients in Treatment and Control Groups.

Characteristics	Total, n = 54	Treatment, n = 27	Control, n = 27	*P*-value
Sex, n (%)				.785
Male	27	14 (51.85)	13 (48.15)	
Female	27	13 (48.15)	14 (51.85)	
Age (years), Mean ± SD	55 ± 13.99	58 ± 14.29	53 ± 13.46	.185
Tumor type, n (%)				.299
Lung cancer	50 (92.59)	24 (88.89)	26 (96.30)	
Colorectal cancer	4 (7.41)	3 (11.11)	1 (3.70)	
EGFRIs drugs, n (%)				.785
Gefitinib	14 (25.93)	7 (25.93)	7 (25.92)	
Icotinib	10 (18.52)	4 (14.81)	6 (22.22)	
Erlotinib	13 (24.07)	7 (25.93)	6 (22.22)	
Afatinib	10 (18.52)	4 (14.81)	6 (22.22)	
Dacomitinib	2 (3.70)	1 (3.70)	1 (3.71)	
Poziotinib	1 (1.85)	1 (3.70)	0	
Cetuximab	4 (7.41)	3 (11.12)	1 (3.71)	
Rash grade, n (%)				.720
Grade 2A	4 (7.41)	3 (11.11)	1 (3.70)	
Grade 2B	24 (44.44)	11 (40.74)	13 (48.15)	
Grade 3A	9 (16.67)	5 (18.52)	4 (14.81)	
Grade 3B	17 (31.48)	8 (29.63)	9 (33.34)	

comparison of rate. All statistical analyses were performed using 2-sided tests, and differences tested were considered statistically significant when $P < .05$. The statistical analysis was performed in the intention-to-treat manner.

Results

The study started on December 1, 2018 and was completed on December 31, 2020. There were 60 patients eligible for screening and 2 patients were excluded. A total of 58 patients were randomized and allocated. Two patients were lost to follow-up in the treatment group and 2 patients were lost to follow-up in the control group because of COVID-19 pandemic, so 54 out of 58 patients completed the study.

A total of 27 (50.0%) male patients and 27 (50.0%) female patients were enrolled. The overall mean age of the patients was 55 (range from 32 to 83) years old. All patients were treated with EGFRIs monotherapy. The median time of EGFRIs-related rash occurrence was 8 days, which was 10 days for patients in the treatment group and 7 days for patients in the control group. There was no statistically significant difference in occurrence time between the 2 groups ($P = .100$). No patient discontinued EGFRIs treatment. The differences between the treatment and control patients in age, gender, tumor type, EGFRIs drugs, and rash grade at baseline were not statistically significant ($P > .05$; Table 1).

Efficacy

Primary endpoints. Of the 58 patients randomized to receive Zhiyang Pingfu Liquid or placebo combined with external hydrocortisone cream and oral minocycline, 27 patients in each group were eligible for analysis. The grade of skin rash was significantly lowered after 14 days treatment in the treatment group ($P < .05$), and the severity was also improved in the control group ($P > .05$).

After 14 days treatment, 22 patients were reported PR with 5 patients NR in the treatment group, while 15 patients were reported PR with 12 patients NR in the control group. The overall curative effect of the treatment group (81.48%) was better than that of the control group (55.56%) in rash grade ($P = .040$; Table 2). The final grading of rash at the end of the study period had no statistical difference between the groups ($P = .194$; Table 3), however, the patients with severe rash in the treatment group was numerically less than that in the control group. The effect comparison of severe rash before and after using Zhiyang Pingfu Liquid in the treatment group is shown in Figure 2, and moderate rash in Figure 3.

Secondary endpoints. The median time of oral minocycline capsules was 7 days for patients in both the treatment and control groups, but the median total dose of minocycline capsules taken by patients in the treatment group was 1000 mg, whereas the median total dose of minocycline capsules taken by patients in the control group was 1400 mg. Of all enrolled patients, only 1 patient in the control group received oral methylprednisolone tablets and minocycline capsules simultaneously because of severe rash with massive infection, pus, and oozing blood. The patient's rash was effectively controlled after 7 days of medication, but the amount of methylprednisolone tablets and minocycline

Table 2. Changes in Rash Grade.

	7 days treatment					14 days treatment				
Group	CR	PR	NR	RR (CR + PR, %)	*P*-value	CR	PR	NR	RR (CR + PR, %)	*P*-value
Treatment	0	14	13	51.85	.413	0	22	5	81.48	.040
Control	0	11	16	40.74		0	15	12	55.56	

Abbreviations: CR, complete response; PR, partial response; NR, no response; RR, response rate.

Table 3. Rash grade After 14 days Treatment.

Group	0	1A	1B	2A	2B	3A	3B	*P*-value
Treatment	0	0	2	12	2	11	0	.194
Control	0	0	0	11	3	9	4	

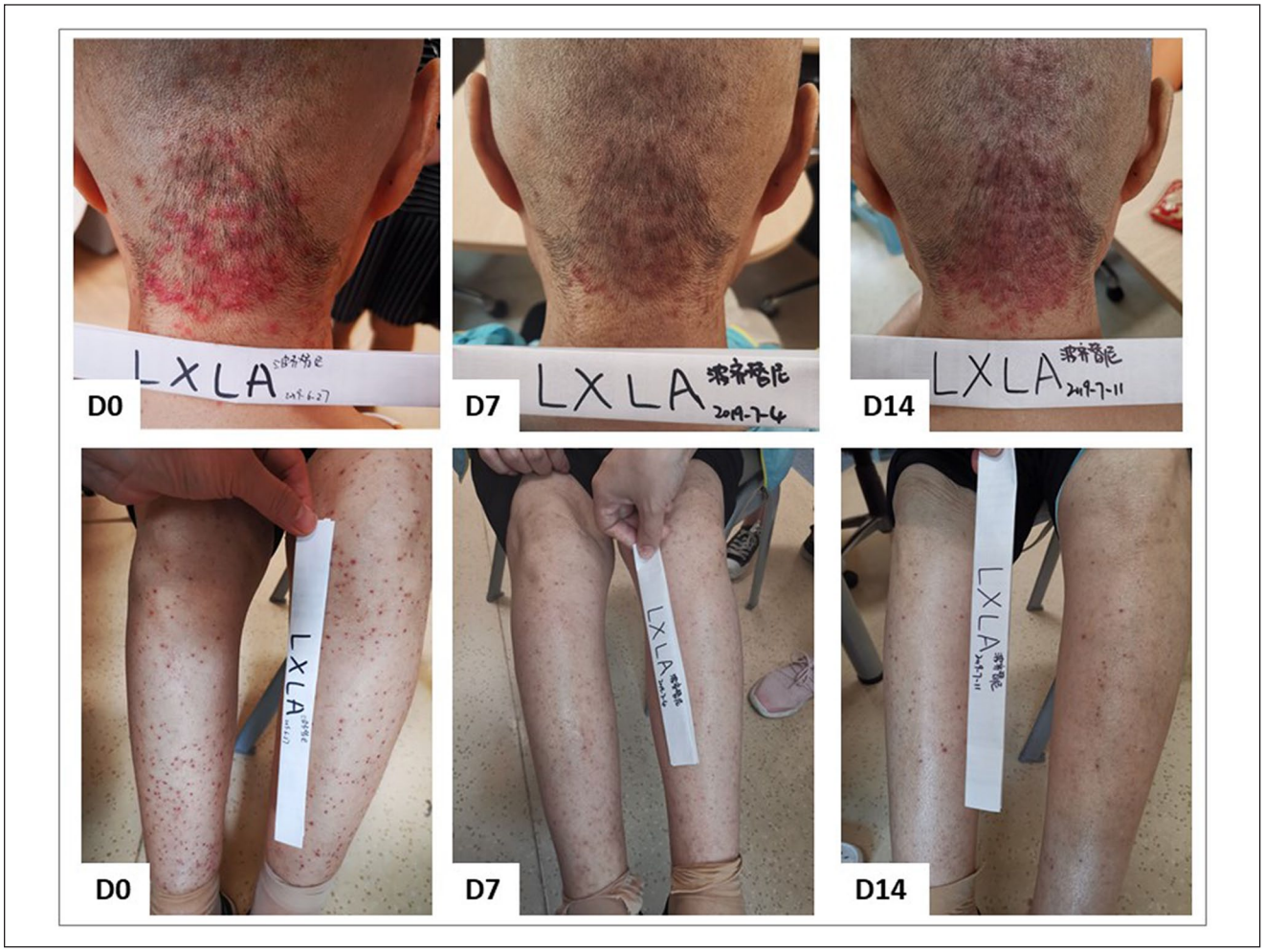

Figure 2. The effect comparison of severe rash before and after using Zhiyang Pingfu Liquid in the treatment group.

capsules was reduced because of severe stomachache. The rash appeared recurrent and reaggravated 3 days after reduction.

There are 24 patients in the treatment group and 23 patients in the control group who suffered from pruritus accompanying rash. Patients' pruritus was evaluated using

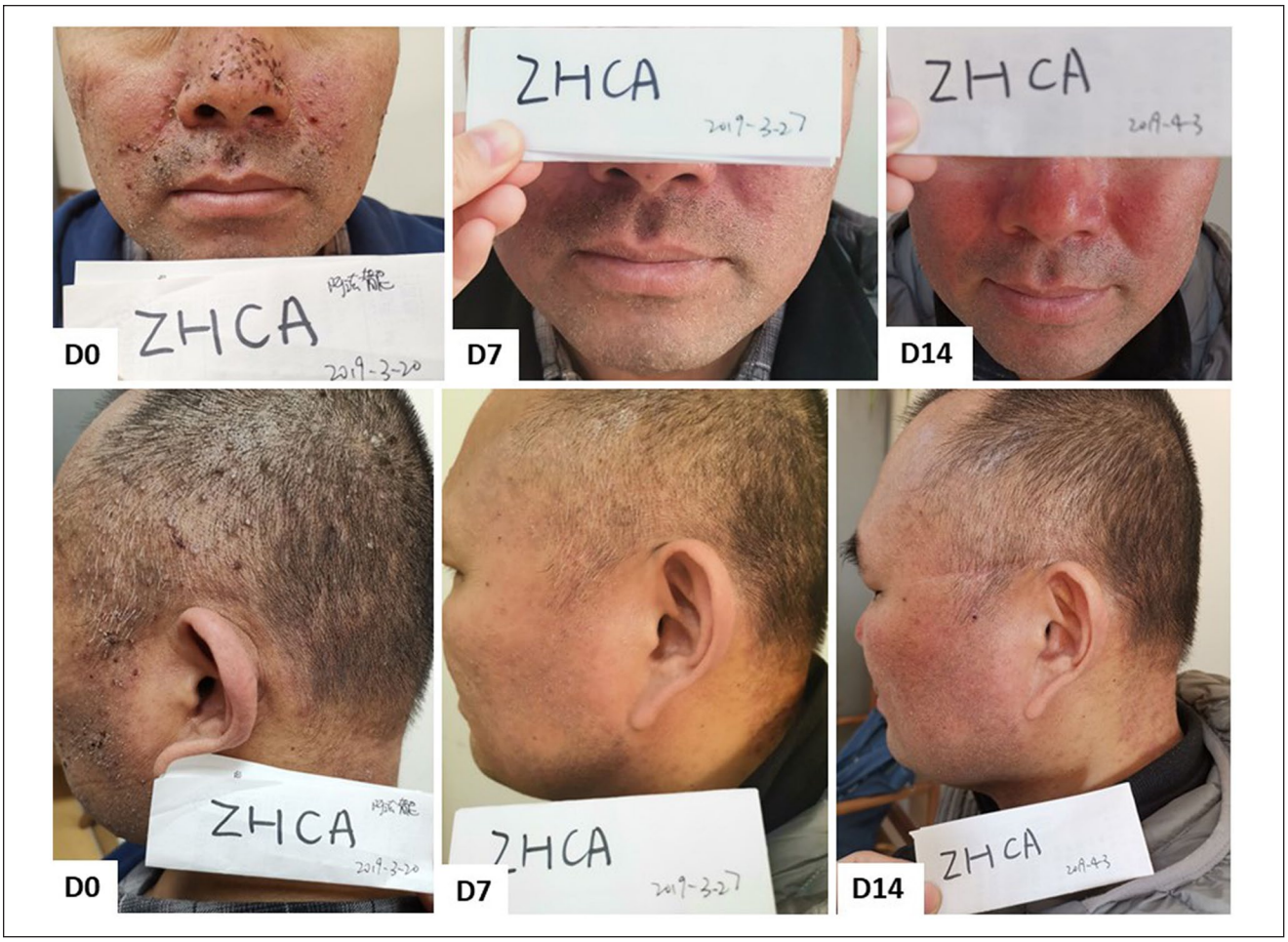

Figure 3. The effect comparison of moderate rash before and after using Zhiyang Pingfu Liquid in the treatment group.

Table 4. Changes in Pruritus Grade.

	7 days treatment					14 days treatment				
Group	CR	PR	NR	RR (CR + PR, %)	*P*-value	CR	PR	NR	RR (CR + PR, %)	*P*-value
Treatment	5	17	2	75.00	.352	9	15	0	100.00	.033
Control	4	15	4	73.91		6	13	4	82.61	

Abbreviations: CR, complete response; PR, partial response; NR, no response; RR, response rate.

the visual analogue scale/ score (VAS). Scores of 1 to 3 were graded as mild, 4 to 6 as moderate, and 7 to 9 as severe. After 14 days treatment, the curative effect of pruritus in the treatment group (100.00%) and control group (82.61%) was comparable ($P = .033$; Table 4).

There were 26 patients in treatment group and 27 patients in control group suffering from skin xerosis. After 14 days treatment, 11 patients were reported CR, and 10 patients were reported PR with 5 patients NR in treatment group, while 10 patients were reported CR, and 9 patients were reported PR with 8 patients NR in control group. The curative effect of the treatment group (80.77%) and control group (70.37%) was comparable ($P > .05$; Table 5).

There were 26 patients in treatment group and 27 patients in control group suffering from paronychia. After 14 days treatment, 9 patients were reported CR, and 1 patient were reported PR with 3 patients NR in treatment group, while 8 patients were reported CR, and 5 patients were reported PR with 6 patients NR in control group. The curative effect of the treatment group (76.92%) and control group (68.42%) was comparable ($P > .05$; Table 6).

Table 5. Changes in Skin Xerosis.

	7 days treatment					14 days treatment				
Group	CR	PR	NR	RR (CR + PR, %)	*P*-value	CR	PR	NR	RR (CR + PR, %)	*P*-value
Treatment	9	9	8	66.67	.842	11	10	5	80.77	.379
Control	11	7	9	60.87		10	9	8	70.37	

Abbreviations: CR, complete response; PR, partial response; NR, no response; RR, response rate.

Table 6. Changes in Paronychia.

	7 days treatment					14 days treatment				
Group	CR	PR	NR	RR (CR + PR, %)	*P*-value	CR	PR	NR	RR (CR + PR, %)	*P*-value
Treatment	9	1	3	76.92	.355	9	1	3	76.92	.355
Control	8	5	6	68.42		8	5	6	68.42	

Abbreviations: CR, complete response; PR, partial response; NR, no response; RR, response rate.

Safety

A total of 4 (14.81%) patients experienced adverse events during this study. Among them, 1 patient (3.70%) in the treatment group experienced the manifestation of poor appetite, 3 patients (11.11%) in the control group experienced stomachache. The adverse events in 4 patients were resolved to disappearance after discontinuation of minocycline capsules or methylprednisolone tablets. It was suggested that these adverse reactions were not directly related to Zhiyang Pingfu Liquid. All enrolled patients during the trial did not experience abnormalities in routine blood tests, liver and renal function, and they experienced no serious or fatal drug-related adverse events.

Discussion

Epidermal growth factor receptor (EGFR) is distributed on the surface of all epithelia including epidermal keratinocytes, outer hair root sheath, and sebaceous glands, and on some mesenchymal derived cell surfaces,[11] while a variety of tumor cells can overexpress EGFR.[12] Therefore, when applying EGFRIs for antitumor targeted therapy, it may also cause specific toxicity to skin and its accessory organs, in which EGFRIs-related rash first occurs.

EGFRIs-related rash usually begins to appear within 1 to 2 weeks after application of EGFRIs, after which the rash gradually aggravates, peaks at 4 to 6 weeks, and begins to gradually resolve at 3 and 4 months.[4] The course of EGFRIs related rash is influenced by the treatment course of EGFRIs drugs. EGFRIs-related rash would be relieved if EGFRIs were discontinued.

EGFRIs-related rash is predominantly papulopustular rashes with a predilection for areas with dense sebaceous gland distribution, such as the head and face, and "V"—shaped areas on the upper part of the trunk, often accompanied by pruritus or even pain. It often starts as papular and erythematous initially, then gradually progresses to pustules, which can scab upon rupture.

Unlike acne vulgaris,[13] EGFRIs related rash has papules and pustules as the main manifestations, mostly accompanied by pruritus or dry skin and, in severe cases, affecting patients' daily life and nocturnal sleep.[14] Whereas acne vulgaris results from inflammation and other secondary reactions that occur in various depths of the hair follicle, the early stage usually presents as white—or black headed comedones with inflammatory papules, nodules, and cysts with pain occasionally, occurring at the site of seborrhea.[15] Both differ in clinical manifestations and pathological features, and the distinction should be noted clinically.[16]

Western medical treatment measures for EGFRIs related rash are mainly through topical or oral antibiotics, topical steroid preparations, and patients with more severe rash are concomitantly treated with oral glucocorticoids.[5] Lichtenberger et al[17] studied 48 patients treated with 8-week prophylactic minocycline for cetuximab-induced cutaneous adverse effects and showed that minocycline helped to reduce the severity of acneiform rash compared with placebo ($P = .05$), while the incidence of rash was not significantly different ($P > .05$). Melosky et al[18] found that the use of minocycline during prophylaxis, at the initial onset of rash and after its severity, had no significant effect on the improvement of rash ($P > .05$).

Since the occurrence of EGFRIs-related rash is related to the continuous application of EGFRIs, the rash tends to be frequent and recurrent, leading to the need for long-term application of antibiotics and glucocorticoids as well. However, it is found in clinical practice that patients experience significant gastrointestinal reactions such as

stomachache and decreased appetite after long-term oral administration of antibiotics, while long-term oral administration of glucocorticoids is associated with more and more significant adverse events.

Therefore, traditional Chinese medicine (TCM) physicians have successively made attempts to use TCM to treat EGFRIs related rash, and a meta-analysis[19] showed that the efficacy of TCM interventions was significant, with significant improvements in patient symptoms and quality of life.

A total of 58 patients with EGFRIs related moderate and severe rash were included in this study, 54 of whom completed the clinical trial, with 27 in each of the treatment and control groups. Previous studies reported EGFRIs-related rash earlier occurrence within 1 to 2 weeks after the initiation of EGFRIs use,[20] and the median onset time of rash in this study was 8 days, which is compatible with the literature.

Based on the results of phase III clinical studies in different EGFRIs, the highest incidence of rash was reported to be around 90% with cetuximab[2] and panitumumab,[21] 75% with erlotinib[22], and approximately 30% with the remaining EGFRIs, gefitinib,[23] icotinib,[24] and Osimertinib.[25] There were only 4 cases of colorectal cancer patients included in this study, all of which were treated with cetuximab and accounted for 7.42% of all enrolled patients.

Statistical analysis showed that the efficacy of the treatment group in treating EGFRIs related moderate to severe rash was superior to that of the control group, and the difference between the 2 groups in the response rate at 14 days of treatment was statistically significant. In addition, the study showed that the median time of taking minocycline capsules was 7 days in both groups, but the median total dosage of minocycline capsules taken by the patients in the treatment group was less than that in the control group, and the number of cases of related adverse events in the treatment group was also less than that in the control group.

After the acute onset rash, the postinflammatory skin alterations, such as erythema and hyperpigmentation in areas previously affected by the papulopustular eruption, will be longterm sequelae that can last for months or years,[4,26] In our study, we also observed this symptom that patients' skin turned red at the second follow-up.

Conclusion

Zhiyang Pingfu Liquid combined with western treatment measures can not only effectively treat EGFRIs related moderate and severe rash and concomitant pruritus, but also reduce the use of minocycline capsules and reduce the adverse events brought by antibiotics. In addition, the application of Zhiyang Pingfu Liquid can make the therapeutic efficacy of rash be effectively maintained with low adverse effects.

For EGFRIs-related moderate to severe rash patients, this study provides a treatment regimen of short-term oral western medicine standard treatment drug minocycline capsules combined with external Zhiyang Pingfu Liquid during the moderate to severe period of rash, until symptoms are relieved and quickly discontinue the western medicine, using Zhiyang Pingfu Liquid for maintenance treatment. The study introduced a new option for patients suffering from EGFRIs-associated rash. However, a larger sample size study is needed to verify this finding.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Trial Registration

This trial was registered at www.chictr.org.cn as ChiCTR1800017053.

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